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"Not Applicable"

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BACKGROUND OF THE INVENTION

[0001] Atherosclerosis is a progressive disease characterized by the thickening, hardening and loss of elasticity of inner artery walls. The pathologic process underlies most coronary heart disease (CHD) and strokes.

[0002] Since atherosclerosis is a leading cause of mortality and morbidity in the world, intense research efforts have been dedicated to the disease for the past two centuries. Many researchers have been focusing on the understanding of atherosclerosis mechanism and the development of efficient screening procedures [1, 2].

[0003] Since Anitschkow, N. stated that dietary cholesterol caused atherosclerosis in 1913, over the past five decades, lipid-lowering therapy has played a central role in the prevention and treatment of atherosclerosis-related CHD or stroke. This therapeutic method treats the elevated level of low-density lipoprotein (LDL) or cholesterol in blood as a primary cause in atherosclerosis [3]. In deciding whether a patient requires the therapy to prevent or to treat the disease, physicians usually rely heavily on measuring the LDL concentration in the patient's blood. The expert panels in the USA, Europe, UK and Canada have defined the guidelines of LDL level in serum [4-7]. It was reported

that there were about 55 million American adults who had elevated level of LDL that warranted intervention [8]. The lipids hypothesis emphasizes a causal relationship between the elevated LDL level and disease. However, clinical evidences indicated that many individuals in the United States developed atherosclerosis-related CHD in the absence of abnormalities in the lipoprotein profile [9].

[0004] The recent method for diagnosing the disease is the so-called the measurement of C-reactive protein (CRP) concentration in blood plasma [9-10]. The method treats atherosclerosis as an inflammatory disease. In 1852, Rokitansky, C.V. suggested that small mural thrombi existed at the arterial wall, which led to plaques. In 1856, Virchow, R. stated that an early event in atherosclerosis was an inflammatory response to an injured arterial wall. In 1973, Ross, R. and Glomset, J. combined the two hypotheses and suggested the response-to-injury hypothesis [11]. The inflammatory hypothesis emphasizes inflammation as a primary cause in atherosclerosis [9-11]. The above-mentioned two major methods for diagnosing the disease are not mutually exclusive but they cannot be united.

[0005] In 1969, Caro, C.G., et al. found that atherosclerotic lesion occurred in areas experiencing low

wall shear stress [12]. In 1980, Texon, M. developed a concept called hemodynamic basis of atherosclerosis [13]. In 1983, Friedman, M.H., et al. stated a causal relationship between arterial geometry and atherosclerosis [14]. Clinical and experimental evidences indicated that the elevated level of heart rate causes atherosclerosis [15-16]. In 1991, Schwartz, C.J., et al. suggested a unifying hypothesis that focused on lesion-prone arterial sites [17]. More recently, Wang, H.H. created analytical models of atherosclerosis [2]. Kruth, H.S. emphasized increased LDL uptake into arterial walls as a primary cause in atherosclerosis [18]. However, there is no screening method that is able to determine the effects of these risk factors on the disease.

[0006] Epidemiological studies stated that many risk factors influenced atherosclerosis, mainly including elevated LDL level, hypertension, smoking cigarette, family history, systemic inflammation such as rheumatoid arthritis, infectious agents such as Chlamydia pneumoniae, high-fat diet and emotion factors such as depression [3, 19]. However, the contributions of these risk factors to the disease cannot be combined using current screening methods, which result in limited reliable clinical screening capabilities. In recent review article entitled "atherosclerosis", Lusis, A.J. points out that efficient screening procedures are

urgently needed but they are unlikely to be available in the near future [19].

BRIEF SUMMARY OF THE INVENTION

[0007] The objective of this invention is to resolve some of the above-mentioned problems by developing a multiparameter method of screening, which is used for predicting a total risk of the disease and a disease risk level, determining a primary cause in the disease, optimizing the therapeutic targets and assessing a therapeutic efficacy for the individuals who require the diagnosis, prevention or treatment of atherosclerosis-related CHD or stroke.

[0008] The method of the invention can be used to combine the contributions of atherosclerotic risk factors to the disease. Screening the LDL level and measuring the CRP concentration in blood, the two major methods for diagnosing the disease, are united into this invention.

[0009] This invention views that atherosclerosis is a multifactor disease with differently combined risk factors dominating at different stages of the disease in different individuals and that the mass transfer flux of LDL and monocyte in blood to the arterial endothelium at the lesion-prone sites is a primary cause in the disease.

Further features and advantages of this invention can be seen in the DETAILED DESCRIPTION OF THE INVENTION.

BRIEF DISCRIPTION OF THE DRAWING

[0010] FIG.1 is a typical input screenshot of the MMA.exe showing the inputted atherosclerotic parameters including a LDL concentration parameter in mg/dL, a CRP concentration parameter in mg/L, a blood systolic pressure parameter in mmHg, a blood diastolic pressure parameter in mmHg, a heart rate parameter in s^{-1}, a plasma temperature parameter in °C, an angle parameter in degree, a radius parameter of the arterial vessels in cm, and an axial position parameter of the diffusional flux in cm, called diffusional length in cm; D_L = the LDL diffusion coefficient in cm^2/s; and D_c = the CRP diffusion coefficient in cm^2/s.

[0011] FIG.2 is a typical output screenshot of the MMA.exe showing the output including a total risk of the disease; a primary cause in the disease; a primary therapy target; a secondary therapy target; and a therapeutic efficacy for individuals who require the diagnosis, prevention or treatment of atherosclerosis-related CHD or stroke.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The present invention is a multiparameter screening method that is used for combining the contributions of atherosclerotic risk factors to the disease, predicting a total risk of the disease and a disease risk level, determining a primary cause in the disease, assessing a therapeutic efficacy and optimizing the therapeutic targets at the different stages of the disease in different individuals who require the diagnosis, prevention or treatment of atherosclerosis-related CHD or stroke, which comprises the following phases:

an individual having the measured values of atherosclerotic parameters;

determining the normal values of these atherosclerotic parameters;

determining the disease risks yielded by the differences between the measured values and the normal values of these atherosclerotic parameters;

adding all the disease risks together so as to yield a total risk of the disease;

determining a disease risk level containing the total risk of the disease;

selecting an atherosclerotic risk factor related to an atherosclerotic parameter that is the greatest contribution to the total risk so as to result in

this risk factor as a primary therapy target of the disease;

determining a greater flux between the LDL mass transfer flux and the monocyte mass transfer flux so as to result in this greater flux as a primary cause in the disease;

selecting a greater concentration level between the LDL level in serum and the CRP level in blood plasma so as to result in this greater level as a secondary therapy target of the disease;

calculating a relative ratio between the current total risk from the currently measured values of these atherosclerotic parameters and the previous total risk from previously measured values of these parameters so as to yield this ratio as a therapeutic efficacy of the disease; and

repeating the above-mentioned methods until the disease risk level is reduced to a normal level for the individual who requires the therapy to prevent or to treat atherosclerosis-related CHD or stroke.

the above-mentioned methods are written as an executable computer program named the MMA.exe to perform said methods.

[0013] The method of this invention comprising the steps of:

[0014] Step one: Determining the mass transfer flux of the LDL particles and monocyte cells in blood to the endothelium at the arterial bifurcations, branching, curvatures or tapering, called the lesion-prone sites, so as to result in this flux as a primary cause in the disease, which comprise:

[0015] Major clinical studies [9-10, 19] state that early atherosclerosis lesions consist of both LDL and monocytes, which are transferred from blood to the arterial endothelium and accumulated in the subendothlium.

[0016] According to these clinical evidences, the inventor has created the multifactor models of atherosclerosis using a bioheterogeneous reaction model, a natural convection model and a boundary value model [1].

[0017] These models view that the mass transfer flux of the LDL and monocytes in blood to the arterial endothelium at the lesion-prone sites is a primary cause in the disease [1].

[0018] These models are used to yield the following expression of the mass transfer flux (detailed derivation

of this expression presented in inventor's notebook and reference [1]):

$$J = 0.69\, c_0 \left(\frac{v^3 D^{16}}{\nu^4}\right)^{\frac{1}{27}} \left(\frac{(g\cos\alpha + f\,u)\,k}{z}\right)^{\frac{2}{9}} \qquad (A)$$

where J = the mass transfer flux of LDL or monocyte, g = the gravitational acceleration, c_0 = the LDL or monocyte concentration in blood, f = the heart rate, v = the eddy of the blood fluid in the region at the lesion-prone sites, u = the average velocity of the blood fluid in axial direction of arterial vessels, ν = the kinetic viscosity of the blood plasma, z = the axial position of diffusional flux along the inner artery wall at the sites or z is called diffusional length, α = the angle between the average velocity and gravity, D = the diffusion coefficient, and $k = \frac{c_0}{\rho_0}\frac{\partial \rho}{\partial c}$ in which ρ = the plasma density and ρ_0 = the blood density.

[0019] These models and expression (A) is used to help the understanding of atherosclerosis mechanism and to explain clinical and experimental results [1], which are supported by the clinical and experimental evidences [2-3, 9-10, 12-21]. This invention involves the expression (A).

[0020] Step two: Defining the atherosclerotic parameters that are related to the atherosclerotic risk factors, which comprise the steps of:

[0021] Since the CRP level in blood plasma is a marker of systemic inflammation or infectious agents [9], the leukocyte-monocyte level in blood has the form:

$$c_0 = H_e c \qquad (B)$$

where c = the CRP concentration or c = the LDL concentration at H_e =1 and H_e = the parameter that is independent of c. Substituting k and (B) into (A) yields:

$$J = A\, c^{\frac{11}{9}} (v^3 D^{16})^{\frac{1}{27}} \left(\frac{g\cos\alpha + f u}{z} \right)^{\frac{2}{9}} \qquad (1.1)$$

where $A = 0.69 H_e^{\frac{11}{9}} \nu^{-\frac{4}{27}} \left(\frac{1}{\rho_0} \frac{\partial \rho}{\partial c} \right)^{\frac{2}{9}}$.

[0022] The Poiseuille law states that the average velocity of a laminar fluid is proportional to the pressure gradient and to the second power of radius of a circular tube, which is expressed by

$$u = H_a p a^2 \qquad (C)$$

where u = the average velocity of blood fluid, p = the blood pressure gradient, a = the radius of arterial vessels and H_a = the parameter that is independent of p and a.

[0023] Since the previous eddy is proportional to the average velocity of the fluid in a circular tube, the eddy has the form

$$v = H_b u \qquad (D)$$

where v = the eddy and H_b is a parameter that is independent of u. Substituting (C) into (D) yields:

$$v = H_a H_b p a^2; \qquad (E)$$

[0024] The Stokes-Einstein equation states that the diffusion coefficient is proportional to the fluid temperature, which has the form

$$D = H_d T \qquad (F)$$

where D = the diffusion coefficient, T = the plasma temperature and H_d = a parameter that is independent of T.

[0025] Substituting (C), (E) and (F) into (1.1) yields

$$J = Bc^{\frac{11}{9}} p^{\frac{1}{3}} T^{\frac{16}{27}} a^{\frac{2}{3}} f^{\frac{2}{9}} z^{-\frac{2}{9}} \qquad (1.2)$$

and

$$J = Ec^{\frac{11}{9}} D^{\frac{16}{27}} z^{-\frac{2}{9}} (\cos\alpha)^{\frac{2}{9}} \qquad (1.3)$$

where J = the mass transfer flux in 10^{-5} g/cm^{2}s; the atherosclerotic parameters including c = the LDL concentration parameter in mg/dL or c = the CRP concentration parameter in mg/L, p = the blood systolic pressure parameter in mmHg or p = the blood diastolic pressure parameter in mmHg, f = the heart rate parameter

in s^{-1}, T = the plasma temperature parameter in °C, α = the angle parameter in degree, a = the radius parameter of arterial vessels in cm, and z = the axial position parameter of diffusional flux in cm or z is called the diffusional length; D = the diffusion coefficient in cm^2/s; the variable $B = AH_a^{\frac{1}{3}} H_b^{\frac{1}{9}} H_d^{\frac{16}{27}}$ that is independent of c, p, T, f, a and z in (1.2); and the variable $E = Agv^{\frac{3}{27}}$ that is independent of c, D, α and z in (1.3).

[0026] The total mass transfer flux given by (1.1) consists of both the flux given by (1.2) under the transient inertial force = ρfu and the flux given by (1.3) under gravity = ρg.

[0027] The inventor defines c, p, T, f, a, α and z in (1.1) or (1.2) and (1.3) as the atherosclerotic parameters because the contributions of atherosclerotic risk factors to the disease are integrated into these expressions through these atherosclerotic parameters.

[0028] Main risk factors of atherosclerosis relate closely to these atherosclerotic parameters. For example, the elevated LDL level equals an increase in the LDL concentration parameter, hypertension risk factor equals an elevated level of the systolic or diastolic pressure parameter, smoking cigarette and depression relate to an

elevated level of heart rate parameter, and the CRP concentration parameter is a marker of the risk factor of systemic inflammation or infectious agents.

[0029] These atherosclerotic parameters and the expressions (1.1) or (1.2) and (1.3) are employed when performing the method of this invention.

[0030] Step three: Determining the disease risks yielded by the difference between the measured values and the normal values of these atherosclerotic parameters, which comprise the steps of:

[0031] Step 3.1:

Substituting a measured value c_m of the LDL concentration parameter into (1.1) yields $J_m = Hc_m^{\frac{11}{9}}$ where $H = A(v^3 D^{16})^{\frac{1}{27}}\left(\frac{g\cos\alpha + fu}{z}\right)^{\frac{2}{9}}$ and H_e = 1 in A;

substituting a normal value c_n of the LDL concentration into (1.1) yields $J_n = Hc_n^{\frac{11}{9}}$; and

calculating $\frac{J_m - J_n}{J_n}$ where $c_m \geq c_n$ yields:

$$R_1 = \left(\frac{c_m}{c_n}\right)^{\frac{11}{9}} - 1 \qquad (1)$$

where R_1 is the disease risk caused by the LDL concentration parameter related to the

atherosclerotic risk factors being an elevated LDL level in human serum, hypercholesterolemia, high-fat diet, or other risk factors that increase in the LDL level.

[0032] Step 3.2:

Substituting a measured value c_m of the CRP concentration parameter into (1.1) yields $J_m = Hc_m^{\frac{11}{9}}$ where $H = A(v^3 D^{16})^{\frac{1}{27}} \left(\frac{g\cos\alpha + fu}{z} \right)^{\frac{2}{9}}$;

substituting a normal value c_n of the CRP concentration into (1.1) yields $J_n = Hc_n^{\frac{11}{9}}$; and calculating $\frac{J_m - J_n}{J_n}$ where $c_m \geq c_n$ yields:

$$R_2 = \left(\frac{c_m}{c_n} \right)^{\frac{11}{9}} - 1 \qquad (2)$$

where R_2 is the disease risk caused by the CRP concentration parameter related to the atherosclerotic risk factors being the systemic inflammation, infectious agents, an elevated CRP level in human blood plasma, or other risk factors that increase the CRP level.

[0033] Step 3.3:

Determining an equivalent factor F between the R_1 in Step 3.1 and the R_2 in Step 3.2, which comprises the following two methods:

1. The first method:

Substituting the LDL diffusion coefficient D_L into

(1.1) yields $J_x = M D_L^{\frac{16}{27}}$ where $M = A c^{\frac{11}{9}} v^{\frac{3}{27}} \left(\frac{g\cos\alpha + f u}{z}\right)^{\frac{2}{9}}$ and

J_x = the LDL mass transfer flux;

substituting the CRP diffusion coefficient D_c into

(1.1) yields $J_y = M D_c^{\frac{16}{27}}$ where J_y = the CRP mass transfer flux;

taking $J_y D_L^{\frac{16}{27}} = J_x D_c^{\frac{16}{27}}$ so as to yield:

$$J_y = J_x F \qquad (G)$$

where the equivalent factor $F = \left(\frac{D_c}{D_L}\right)^{\frac{16}{27}}$; and

according to (G), the equation (2) in Step 3.2 is rewritten as

$$R_2 = F\left(\left(\frac{c_m}{c_n}\right)^{\frac{11}{9}} - 1\right) \qquad (3)$$

where the disease risk R_2 caused by the difference between the measured value c_m and normal value c_n of the CRP concentration parameter corresponds to the disease risk R_1 caused by the LDL concentration parameter by means of (3).

2. The secondary method:

The equivalent factor F = 0.66, which will be yielded in the Step five of the DETAILED DESCRIPTION OF THE INVENTION.

[0034] Step 3.4:

Substituting a measured value p_m of the blood systolic pressure parameter into (1.2) yields $J_m = H_p p_m^{\frac{1}{3}}$ where $H_p = Bc^{\frac{11}{9}} T^{\frac{16}{27}} a^{\frac{2}{3}} f^{\frac{2}{9}} z^{-\frac{2}{9}}$;

substituting a normal value p_n of the systolic pressure into (1.2) yields $J_n = H_p p_n^{\frac{1}{3}}$; and

calculating $\frac{J_m - J_n}{J_n}$ where $p_m \geq p_n$ yields:

$$R_4 = \left(\frac{p_m}{p_n}\right)^{\frac{1}{3}} - 1 \qquad (4)$$

where R_4 is the disease risk caused by the systolic pressure parameter related to atherosclerotic risk factors being an elevated level of the systolic pressure, family history of hypertension, or other risk factors that increase in the systolic pressure.

[0035] Step 3.5:

Substituting a measured value p_m of the blood diastolic pressure parameter into (1.2) yields $J_m = H_p p_m^{\frac{1}{3}}$ where $H_p = Bc^{\frac{11}{9}} T^{\frac{16}{27}} a^{\frac{2}{3}} f^{\frac{2}{9}} z^{-\frac{2}{9}}$; substituting a normal value p_n of the diastolic pressure into (1.2) yields $J_n = H_p p_n^{\frac{1}{3}}$; and calculating $\frac{J_m - J_n}{J_n}$ where $p_m \geq p_n$ yields:

$$R_5 = \left(\frac{p_m}{p_n}\right)^{\frac{1}{3}} - 1 \qquad (5)$$

where R_5 is the disease risk caused by the diastolic pressure parameter related to the atherosclerotic risk factors being an elevated level of the diastolic pressure, the family history of hypertension, or other risk factors that increase in the diastolic pressure.

[0036] Step 3.6:

Substituting a measured value f_m of the heart rate parameter into (1.2) yields $J_m = H_f f_m^{\frac{2}{9}}$ where $H_f = Bc^{\frac{11}{9}} T^{\frac{16}{27}} a^{\frac{2}{3}} p^{\frac{1}{3}} z^{-\frac{2}{9}}$; substituting a normal value f_n of the heart rate into (1.2) yields $J_n = H_f f_n^{\frac{2}{9}}$; and calculating $\frac{J_m - J_n}{J_n}$ where $f_m \geq f_n$ yields:

$$R_6 = \left(\frac{f_m}{f_n}\right)^{\frac{2}{9}} - 1 \qquad (6)$$

where R_6 is the disease risk caused by the heart rate parameter related to the atherosclerotic risk factors being an elevated level of the heart rate, smoking cigarette, emotional factors such as depression, or other risk factors that increase the heart rate.

[0037] Step 3.7:

Substituting a measured value a_m of the radius parameter of arterial vessel into (1.2) yields $J_m = H_a a_m^{\frac{2}{3}}$ where $H_a = Bc^{\frac{11}{9}} T^{\frac{16}{27}} f^{\frac{2}{9}} p^{\frac{1}{3}} z^{-\frac{2}{9}}$;

substituting a normal value a_n of the arterial radius into (1.2) yields $J_n = H_a a_n^{\frac{2}{3}}$; and

calculating $\frac{J_m - J_n}{J_n}$ where $a_m \geq a_n$ yields:

$$R_7 = \left(\frac{a_m}{a_n}\right)^{\frac{2}{3}} - 1 \qquad (7)$$

where R_7 is the disease risk caused by the arterial radius parameter related to atherosclerotic risk factors being the increased radius of arterial vessels at the lesion-prone sites, or other risk factors that increase the arterial radius.

[0038] Step 3.8:

Substituting a measured value T_m of the plasma temperature parameter into (1.2) yields $J_m = H_T T_m^{\frac{16}{27}}$ where $H_T = Bc^{\frac{11}{9}} a^{\frac{2}{3}} f^{\frac{2}{9}} p^{\frac{1}{3}} z^{-\frac{2}{9}}$;

substituting a normal value T_n of the plasma temperature into (1.2) yields $J_n = H_T T_n^{\frac{16}{27}}$; and

calculating $\frac{J_m - J_n}{J_n}$ where $T_m \geq T_n$ yields:

$$R_8 = \left(\frac{T_m}{T_n}\right)^{\frac{16}{27}} - 1 \qquad (8)$$

where R_8 is the disease risk caused by the plasma temperature parameter related to the atherosclerotic risk factors being the elevated temperature of the blood plasma in the region of the lesion-prone sites, the elevated body temperature-related diseases, or other risk factors that increase the plasma temperature.

[0039] Step 3.9:

Substituting a measured value α_m of the angle parameter into (1.3) yields $J_m = H_\alpha (\cos\alpha_m)^{\frac{2}{9}}$ where $H_\alpha = Ec^{\frac{11}{9}} D^{\frac{16}{27}} z^{-\frac{2}{9}}$;

substituting a normal value α_n of the angle into (1.3) yields $J_n = H_\alpha (\cos\alpha_n)^{\frac{2}{9}}$; and

calculating $\frac{J_m - J_n}{J_n}$ where $\alpha_n \geq \alpha_m$ yields:

$$R_9 = \left(\frac{\cos\alpha_m}{\cos\alpha_n}\right)^{\frac{2}{9}} - 1 \qquad (9)$$

where R_9 is the disease risk caused by the angle parameter related to the atherosclerotic risk factors being the reduced size of the angle between the gravity and the average velocity of blood fluid in the region of the lesion-prone sites, an acute daughter angle of arterial bifurcation, or other risk factors that reduce the angle size.

[0040] Step 3.10:

Substituting a measure value z_m of the axial position parameter of the diffusional flux into (1.1) yields $J_m = H_z z_m^{-\frac{2}{9}}$ where $H_z = Ac^{\frac{11}{9}}(v^3 D^{16})^{\frac{1}{27}}(g\cos\alpha + fu)^{\frac{2}{9}}$; substituting a normal value z_n of the diffusional length into (1.1) yields $J_n = H_z z_n^{-\frac{2}{9}}$; and calculating $\frac{J_m - J_n}{J_n}$ where $z_m \leq z_n$ yields:

$$R_{10} = \left(\frac{z_n}{z_m}\right)^{\frac{2}{9}} - 1 \qquad (10)$$

where R_{10} is the disease risk caused by the axial position parameter of diffusional flux related to the atherosclerotic risk factors being the

reduced axial position of the diffusional flux along the inner arterial wall at the lesion-prone sites, or other risk factors that reduce the axial position.

[0041] Step four: Adding the R_1 in step 3.1 and the R_2 in step 3.3 through the R_{10} in step 3.10 together so as to yield a total risk of the disease comprising;

a current total risk of the disease caused by the differences between the currently measured values and the normal values of the atherosclerotic parameters;

a previous total risk of the disease caused by the differences between the previously measured values and the normal values of the atherosclerotic parameters.

[0042] Step five: Determining a disease risk level containing the total risk of the disease in Step four comprising;

considering the range of the LDL concentration in serum from 100 mg/dL to 300 mg/dL; and

dividing the LDL risk level into the six risk sublevels at intervals of 33 mg/dL according to the guideline of LDL risk level given by the expert panels on US National Cholesterol Education Program;

considering the range of CRP concentration in blood plasma from 1.0 mg/L to 4.0 mg/L; and

dividing the CRP risk level into the six risk sublevels at intervals of 0.5 mg/L according to the guideline of the CRP risk level given by American Heart Association;

calculating the ratio between the LDL range and the CRP range yields an equivalent factor F = 2/3 = 0.66;

Substituting the F = 0.66, c_n = 1.0 mg/L and the six CRP measured vales that equal the interval values of six CRP risk sublevels into the equation (3) in Step 3.3 respectively; and

calculating (3) yields the six disease risks as the interval values of the six disease risk sublevels respectively;

doubling these interval values so as to result in the following seven disease risk sublevels caused by combining the LDL flux and the monocyte flux: 0.84 ≥ first disease risk level ≥ 0.00, 1.75 ≥ second disease risk level > 0.84, 2.70 ≥ third disease risk level > 1.75, 3.70 ≥ fourth disease risk level > 2.70, 4.70 ≥ fifth disease risk level > 3.70, 5.80 ≥ sixth disease risk level > 4.70 and seventh disease risk level > 5.80; and

selecting a disease risk level containing the total risk of the disease in Step four from among seven of the disease risk sublevels.

[0043] Step six: Selecting an atherosclerotic risk factor related to the atherosclerotic parameter that is the greatest contribution to the total risk of the disease in Step four so as to result in this risk factor as a primary therapy target of the disease.

[0044] Step seven: selecting a greater flux between the LDL mass transfer flux and the monocyte mass transfer flux so as to result in this greater flux as a primary cause in the disease, said method comprising the steps of:

selecting the LDL mass transfer flux as a primary cause in the disease when R_1 in Step 3.1 $\geq$ R_2 in Step 3.3; or

selecting the monocyte mass transfer flux as a primary cause in the disease when R_1 in Step 3.1 $<$ R_2 in Step 3.3;

[0045] Step eight: Selecting an greater level between a measured value of the LDL concentration parameter in Step 3.1 and a measured value of the CRP concentration parameter in Step 3.2 so as to result in this greater

level as a secondary therapy target of the disease, said method comprising the steps of:

selecting the LDL concentration level in serum as a secondary therapy target of the disease when R_1 in Step 3.1 $\geq$ R_2 in Step 3.3; or

selecting the CRP concentration level in blood plasma as a secondary therapy target of the disease when R_1 in Step 3.1 $<$ R_2 in Step 3.3;

[0046] Step nine: Calculating a relative ratio between the current total risk of the disease and the previous total risk of the disease in Step four so as to yield this ratio as a therapeutic efficacy of the disease.

[0047] Step ten: Repeating the method in Step three through the method in Step nine until the disease risk level is reduced to a normal level for the individual who requires the therapy to prevent or to treat atherosclerosis-related CHD or stroke.

[0048] Step eleven: These methods in Step three through Step nine are written as an executable computer program named said MMA.exe that provides greater ease and convenience to perform these methods.

[0049] EXAMPLES:

[0050] Example 1. An individual having a measured value of the LDL level in serum of 150 mg/dL and a measured value of the CRP concentration in blood plasma of 2.3 mg/L.

[0051] Inputting these measured values into said MMA.exe so as to yield the following first output for the individual: a total risk of the disease is 1.82 or 182% in which the disease risk caused by the LDL concentration parameter is 0.64 or 64% and the disease risk caused by the CRP concentration parameter is 1.18 or 118%; a third disease risk level; a primary cause in disease being the monocyte mass transfer flux; a primary therapy target being systemic inflammation such as rheumatoid arthritis, infectious agents or other risk factors that increase the CRP level.

[0052] After treating systemic inflammation, the patient's CRP level is reduced to 1.6 mg/L from 2.3 mg/L and the following second output yielded by said MMA.exe: a total risk of the disease is 1.16 or 116% in which the disease risk caused by the CRP level is reduced to 0.52 from 1.18; a second disease risk level; a primary cause in disease being the LDL mass transfer flux; a therapeutic efficiency of 36.32%; a primary therapy target being the elevated LDL level in blood, high-fat diet or other risk factors that increase the LDL level.

[0053] This example shows that the method of this invention can be widely used for clinical practices in atherosclerosis-related CHD or stroke because screening the LDL level and measuring the CRP level in blood, the two major methods for diagnosing the disease, have been united into this invention.

[0054] Example 2. An individual having a measured value of the LDL concentration in serum of 110 mg/dL, a measured value of blood systolic pressure of 195 mmHg, a measured heart rate of 85 s^{-1} and a measured value of the CRP level in blood plasma of 1.2 mg/L.

[0055] Inputting these measured values into said MMA.exe so as to yield the following first output for the individual: a total risk of the disease of 0.503 or 50.3%; a first disease risk level; a primary cause in disease being the monocyte mass transfer flux; a primary therapy target being the elevated level of the systolic pressure, the family history of hypertension or other risk factors that increase the systolic pressure; a secondary therapy target being the systemic inflammation or other risk factors that increase the CRP level.

[0056] After treating the hypertension, the individual's systolic pressure is reduced to 160 mmHg from 195 mmHg

and the following second output yielded by said MMA.exe: a total risk of the disease is reduced to 0.428 or 42.8% from 0.503 or 50.3%; a first disease risk level; a primary cause in the disease being the monocyte mass transfer flux; a therapeutic efficacy of 14.9%, a primary therapy target being the systemic inflammation or other risk factors that increase the CRP level; and a secondary therapy target being the elevated LDL level in blood or other risk factors that increase the LDL level.

[0057] This example shows that the method of this invention is reliable because it can be used to combine the contributions of multiple risk factors of atherosclerosis to the disease.

[0058] Example 3. The major clinical study [20] stated that a 1.0% reduction in an individual's total LDL level in blood led to a 1.5% reduction in the risk of atherosclerosis-related CHD. Said MMA.exe yields that a 1.0% reduction in the LDL level results in a 1.22% reduction in this risk. This example indicates that the method of this invention is strongly supported by the clinical evidence.

[0059] Example 4. Autopsy and clinical studies [13-14, 17, 21] suggested that regions of arterial bifurcations had the greatest predilection for atherosclerosis.

However, no screening method is able to determine the contribution of the arterial geometry to the disease. Internal angles among 70 human aortic bifurcations can vary widely from 10° to 70° [22]. Different internal angles may lead to different angle α in (1.3).

[0060] An individual A having a measured angle α_1 being 15°, an individual B having a measured angle α_2 being 45° and the two persons having a 1% increase in the LDL level in blood. Using said MMA.exe, this invention predicts a 7.2% lower total risk for 45° than for 15°. This risk from difference in the bifurcation's internal angles is significantly lower than the 1.5% reduction in risk from 1% reduction in LDL level [20], which indicates that the arterial geometry in certain instances can play a greater role in atherosclerosis than simply LDL level.

[0061] In the example, the method of this invention reveals that atherosclerosis is a multifactor disease with differently combined risk factors dominating in different individuals.

[0062] Example 5. The first step is inputting the currently measured values, the previously measured values and the normal values of the individual's atherosclerosis parameters into the input screen of said MMA.exe showing in FIG. 1. The second step is pressing the "update"

button and "calc. risk" button of the input screen and finally, pressing the "evaluate" button of the output screen so as to yield a typical output screen showing in FIG. 2

[0063] This output from said MMA.exe containing a total risk of the disease; a primary cause in the disease; a primary therapy target; a secondary therapy target; and a therapeutic efficacy for individuals who require the therapy to prevent or treat atherosclerosis-related CHD or stroke.

[0064] This example indicates that said MMA.exe can perform this method of this invention with greater ease and convenient.

[0065] THE MAIN ADVANTAGES OF THE INVENTION ARE:

[0066] The method of this invention allows physician to predict a total risk of the disease and a disease risk level; to determine a primary cause in the disease; to assess the therapeutic efficacy and to optimize the therapeutic targets at the different stages of disease in different individuals who require the diagnosis, the prevention or the treatment of atherosclerosis-related CHD or stroke.

[0067] The method of this invention is reliability because it can be used to combine the contributions of atherosclerotic risk factors to the disease.

[0068] The method of this invention is efficient because it views atherosclerosis-related CHD or stroke as a multifactor disease with differently combined risk factors dominating at the different stages of disease in different individuals, which is supported by major clinical and experimental evidences [3, 10, 13-21].

[0069] The method of this invention can be widely used for the clinical practices in atherosclerosis-related CHD or stroke because screening the LDL level and measuring the CRP concentration in blood, the two major methods for diagnosing the disease, have been united into this invention.

[0070] The method of the invention is written as an executable computer program named said MMA.exe that provides greater ease and convenience to perform this method.

[0071] While a specific embodiment of the invention has been show and described in detail to illustrate the application of the principles of the invention, it will be understood that the invention may be embodied

otherwise without departing from such principles and that various screening methods, alternative executable computer program, and equivalents will occur to those skilled in the art given the benefit of this disclosure. Thus, the invention is not limited to the specific embodiment described herein, but is defined by the appended claims.